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## ARTIGO ORIGINAL

### Prevalência e susceptibilidade antimicrobiana de uropatógenos isolados de infecções ambulatoriais e nosocomiais em Nova Friburgo, Rio de Janeiro, Brasil

*Prevalence and antimicrobial susceptibility of uropathogens isolated from ambulatory and nosocomial infections at Nova Friburgo, Rio de Janeiro, Brazil*

*Prevalencia y susceptibilidad antimicrobiana de uropatógenos aislados de infecciones ambulatorias y nosocomiales en Nova Friburgo, Rio de Janeiro, Brasil*

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## RESUMO

**Justificativa e Objetivos:** Infecção do Trato Urinário (ITU) é a segunda infecção mais comum, geralmente causada por enterobactérias, principalmente *Escherichia coli*. Estes microrganismos tem apresentado resistência antimicrobiana para as principais drogas utilizadas para tratar ITU em diferentes partes do mundo. Entretanto, estudos prévios sobre a prevalência e susceptibilidade antimicrobiana regional não foram publicados. Este trabalho objetivou investigar a prevalência e susceptibilidade aos antimicrobianos apresentado por bactérias associadas a ITU de pacientes ambulatoriais ou nosocomiais atendidos ou internados em um hospital em Nova Friburgo, Rio de Janeiro, Brasil. **Métodos:** Um estudo retrospectivo avaliou a prevalência e a susceptibilidade antimicrobiana de urinoculturas positivas de pacientes ambulatoriais e nosocomiais entre Julho de 2010 a Junho de 2014. **Resultados:** Dos pacientes ambulatoriais, o microrganismo mais prevalente foi *Escherichia coli* (76.50%), seguido por *Enterobacter* sp. (12.02%), e *Proteus* sp. (5.46%). Nas ITUs nosocomiais, as bactérias mais prevalentes foram *E. coli* (65.96%), *Proteus* sp. (7.80%), e *Pseudomonas* sp. (7.09%). A maioria das urinoculturas positivas foi isolada de mulheres (89.13%). A susceptibilidade antimicrobiana revelou que a maioria de *E. coli* isolada de pacientes ambulatoriais foi mais resistente à ampicilina (45.00%), ácido nalidíxico (37.14%), nitrofurantoína (35.71%). Dos isolados nosocomiais, *E. coli* foi mais resistente à ampicilina (56.69%), cefalotina, trimetoprim/sulfametoxazol (43.01%) e ciprofloxacina (33.33%). **Conclusão:** A resistência antimicrobiana de *E. coli* foi observada na maioria das ITUs, independente da origem do paciente. Estes resultados contribuirão para melhorar a seleção da terapia antimicrobiana adequada tanto para ITU ambulatorial quanto hospitalar adquiridas em nossa comunidade.

**Descritores:** Resistência Microbiana a Drogas. Enterobacteriaceae. *Escherichia coli*. Infecção do Trato Urinário.

## ABSTRACT

**Background and Objectives:** Urinary tract infection (UTI) is the second most common infection, usually caused by enterobacteria, mainly *Escherichia coli*. These microorganisms have shown antibiotic resistance to several drugs used to treat UTI in different parts of the world. However, previous studies on regional prevalence and antimicrobial susceptibility have not been published. This work aimed to investigate the prevalence and antimicrobial susceptibility of bacteria associated to UTI of out- and nosocomial patients examined and/or treated in a hospital at Nova Friburgo, Rio de Janeiro, Brazil. **Methods:** A retrospective study evaluated the prevalence and antimicrobial susceptibility of positive urine cultures isolated from out-and nosocomial patients from July 2010 to June 2014. **Results:** From outpatients, the most

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prevalent microorganism was *Escherichia coli* (76.50%) followed by *Enterobacter* sp. (12.02%) and *Proteus* sp. (5.46%). In nosocomial UTIs, the most prevalent bacteria were *E. coli* (65.96%), *Proteus* sp. (7.80%), and *Pseudomonas* sp. (7.09%). Most of positive urine cultures were isolated from women (89.13%). The antimicrobial susceptibility revealed that most of *E. coli* isolated from outpatients, were resistant to ampicillin (45.00%), nalidixic acid (37.14%) and nitrofurantoin (35.71%). For nosocomial isolates, most of *E. coli* were resistant to ampicillin (56.69%), cephalothin, trimethoprim/sulfamethoxazole (43.01%), and ciprofloxacin (33.33%). **Conclusion:** *E. coli* antimicrobial resistance was observed in most of UTI, independently of patient origin. These data should contribute to improve the selection of adequate antimicrobial treatment for both hospital and ambulatorial-acquired UTIs in our community.

**Keywords:** Drug Resistance, Microbial. Enterobacteriaceae. *Escherichia coli*. Urinary Tract Infection.

## RESUMEN

**Antecedentes y Objetivos:** La infección del tracto urinario (ITU) es la segunda infección más común, generalmente causada por enterobacterias, principalmente *Escherichia coli*. Estos microorganismos demostraron resistencia a las principales drogas utilizadas para tratar ITU en diferentes partes del mundo. Sin embargo, no fueron publicados estudios previos sobre prevalencia y susceptibilidad antimicrobiana regional. Se objetivó investigar prevalencia y susceptibilidad antimicrobiana presentada por bacterias asociadas a ITU de pacientes ambulatorios o nosocomiales atendidos o internados en un hospital de Nova Friburgo, Rio de Janeiro, Brasil. **Métodos:** Un estudio retrospectivo evaluó prevalencia y susceptibilidad antimicrobiana de urocultivos positivos de pacientes nosocomiales y ambulatorios entre julio 2010 y junio 2014. **Resultados:** Entre los pacientes ambulatorios, el microorganismo prevalente fue *Escherichia coli* (76,50%), seguido de *Enterobacter* sp. (12,2%), y *Proteus* sp. (5,46%). En las ITU nosocomiales, las bacterias prevalentes fueron *E. coli* (65,96%), *Proteus* sp. (7,80%) y *Pseudomonas* sp. (7,09%). La mayoría de los urocultivos positivos fueron aislados de mujeres (89,13%). La susceptibilidad antimicrobiana reveló que la mayoría de *E. coli* de pacientes ambulatorios fue más resistente a ampicilina (45,00%), ácido nalidixico (37,14%) y nitrofurantoína (35,71%). De los cultivos nosocomiales, *E. coli* fue más resistente a ampicilina (56,69%), cefalotina, trimetoprima/sulfametoxazol (43,01%) y ciprofloxacina (33,33%). **Conclusión:** Se observó resistencia antimicrobiana de *E. coli* en la mayoría de las ITUs, independientemente del origen del paciente. Los resultados contribuirán a seleccionar terapia antimicrobiana adecuada para ITUs ambulatorias y hospitalarias adquiridas en nuestra comunidad.

**Palabras clave:** Resistencia microbiana a las drogas. Enterobacteriaceae. *Escherichia coli*. Infección del tracto urinario.

## INTRODUCTION

Urinary tract infection (UTI) is among the most common infectious diseases of humans and is the most common nosocomial infection in the developed world. The health care costs to treat UTI are approximately US\$3.5 billion per year in the United States alone. Moreover, complications caused by frequent antimicrobial use, such as high-level antibiotic resistance, have brought worries.<sup>1,2</sup>

UTIs are defined as the microbial colonization and tissue invasion of any part of the urinary tract, from the urethra to the kidneys.<sup>3</sup> The frequency of the microorganisms involved in a UTI diagnosis depends on the place where the infection was acquired. For example, it will differ if the infections are intra or extra-nosocomial and it also differs for each hospital environment.<sup>4</sup>

The majority of these infections are caused by *Enterobacteriaceae*, mainly *Escherichia coli* which isolation rate varies from 70% to 90% from acute outpatient UTIs and 50% from hospital-acquired UTIs.<sup>5</sup>

The bacteria may infect the urethra and migrate to the kidney or prostate.<sup>6</sup> Clinical conditions such as immunosuppression, surgical manipulations, urinary tract malformations, and catheters may predispose patients to nosocomial infection by microorganisms that, usually, are not uropathogenic.<sup>7</sup>

The global dissemination of drug-resistant organisms is troublesome for medical practitioners because it decreases the available options for appropriate treatment. This contributes to increased patient morbidity and mortality. The global spread of drug resistance was recently recognized as a major threat to human health.<sup>8</sup>

For *E. coli*, the high reported resistance to fluoroquinolones means limitations to available oral treatment for conditions which are common in the community, such as urinary tract infections.<sup>9</sup>

Thus, this study aimed to investigate the prevalence and antimicrobial susceptibility of bacteria associated to UTI of out- and nosocomial patients examined and/or treated in a hospital at Nova Friburgo, Rio de Janeiro, Brazil.

## METHODS

This was a retrospective cross-sectional study conducted by collecting previously recorded data about UTIs microbiological cultures and antimicrobial susceptibility tests realized at the clinical laboratory of Casa de Saúde São Lucas, a private hospital in Nova Friburgo, Rio de Janeiro, Brazil.

The study and data access was authorized by the hospital Laboratory Technical Director, following the ethical principles described at Resolution No. 196/96 of the National Health Council/Ministry of Health of Brazil.

Outpatient urine cultures data were collected from November 2013 to May 2014 while hospitalized patients data were collected in two different periods, from July 2010 to November 2012 and July 2013 to June 2014.

All microorganisms were previously identified following techniques described by KONEMAN et al. (2008).<sup>10</sup> Sensitivity testing was performed by disk diffusion method according to the CLSI (Clinical and Laboratory Standards Institute, 2010).<sup>11</sup> The data was analyzed and the results expressed as percentage.

## RESULTS

A total of 2223 urine culture data were investigated. From the total, 1592 (71.61%) were from outpatients and 631 (28.39%) were from nosocomial patients.

From 1592 urine cultures from outpatients, 317 were positive (11.37%), while in the hospital setting, from the total of 613 urine samples, 136 (21.55%) were positive.

Females were more affected in both nosocomial (67.65%) and ambulatorial (89.50%) settings (Table 1). The age group of outpatients with positive cultures ranged from 0 to 92 years old. The overall prevalence was found in 13 to 40 year-olds, which comprised 45.86% of the cases (Table 1).

**Table 1.** Positivity of Urine Culture According to gender and age of outpatients.

Age (years)	Gender		Total n (%)
	Female n (%)	Male n (%)	
< 1	2 (1.23)	2 (10.53)	4 (2.21)
1-12	5 (3.09)	2 (10.53)	7 (3.87)
13-40	77 (47.53)	6 (31.58)	83 (45.86)
41-64	52 (32.10)	1 (5.26)	53 (29.28)
> 65	26 (16.05)	8 (42.10)	34 (18.78)
Total	162 (100)	19 (100)	181 (100)

In the outpatient setting, the most prevalent bacteria was *E. coli* (76.50%), followed by *Enterobacter* sp. (12.02%) and *Proteus* sp. (5.46%). In nosocomial UTIs, the most prevalent microorganism was *E. coli* (65.96%), followed by *Proteus* sp. (7.80%) and *Pseudomonas* sp. (7.09%) (Table 2).

Antimicrobial susceptibility test results of the 3 most prevalent bacteria isolated from outpatients are shown at table 3. *E. coli* isolates showed resistance to most of antibiotic tested, such as ampicillin (45.00%), nalidixic acid (37.14%), nitrofurantoin (35.71%), and pipemidic acid (32.86%). *Enterobacter* sp. isolates

were resistant to ampicillin (95.45%), cephalexin and nitrofurantoin (77.27%). *Proteus* sp. showed resistance to nitrofurantoin (100%), ampicillin (90%) and trimethoprim/sulfamethoxazole (40%) (Table 3).

**Table 3.** Resistance profile of uropathogens isolated from outpatient samples in Nova Friburgo, from November 2013 to May 2014.

Antimicrobial	<i>E. coli</i> (140)	<i>Enterobacter</i> sp. (22)	<i>Proteus</i> sp. (10)
	n (%)	n (%)	n (%)
Ampicillin	63 (45.00)	21 (95.45)	9 (90.00)
Cefaclor	19 (13.57)	11 (50.00)	1 (10.00)
Ceftriaxone	5 (3.57)	3 (13.64)	1 (10.00)
Cefuroxime	10 (7.14)	7 (31.82)	2 (20.00)
Cephalexin	27 (19.29)	17 (77.27)	6 (60.00)
Ciprofloxacin	29 (20.71)	3 (13.64)	2 (20.00)
Gentamicin	9 (6.43)	2 (9.09)	1 (10.00)
Nalidixic acid	52 (37.14)	12 (54.55)	3 (30.00)
Nitrofurantoin	50 (35.71)	17 (77.27)	10 (100)
Norfloxacin	29 (20.71)	3 (13.64)	2 (20.00)
Ofloxacin	26 (18.57)	4 (18.18)	1 (10.00)
Pipemidic acid	46 (32.86)	10 (45.45)	2 (20.00)
Trimethoprim/ Sulfamethoxazole	34 (24.29)	11 (50.00)	4 (40.00)

Antimicrobial susceptibility test results of the 3 most prevalent bacteria isolated from nosocomial patients are shown at table 4. *E. coli* was again resistant to most of antibiotic tested, including ampicillin (56.69%), cephalothin, trimethoprim/sulfamethoxazole (43.01%), and ciprofloxacin (33.33%). *Proteus* sp. was resistant to ampicillin (72.73%), amoxicillin/clavulanic acid, cephalothin and trimethoprim/sulfamethoxazole (54.55%). *Pseudomonas* sp. showed resistance to trimethoprim/sulfamethoxazole (90%), cephalothin, nitrofurantoin (70%) and amoxicillin/clavulanic acid (60%) (Table 4).

**Table 2.** Microorganisms isolated from out-and nosocomial patients at Nova Friburgo, RJ, Brazil.

Uropathogen	Outpatients			Nosocomial patients		
	Male n (%)	Female n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
<i>E. coli</i>	9 (45.00)	131 (80.37)	140 (76.50)	24 (51.06)	69 (73.40)	93 (65.96)
<i>Enterobacter</i> sp.	5 (25.00)	17 (10.43)	22 (12.02)	3 (6.38)	6 (6.38)	9 (6.38)
<i>Proteus</i> sp.	3 (15.00)	7 (4.30)	10 (5.46)	4 (8.51)	7 (7.45)	11 (7.80)
<i>Pseudomonas</i> sp.	1 (5.00)	1 (0.61)	2 (1.09)	7 (14.89)	3 (3.19)	10 (7.09)
<i>Klebsiella</i> sp.	2 (10.00)	3 (1.84)	5 (2.73)	5 (10.64)	3 (3.19)	8 (5.67)
<i>S. aureus</i>	0 (0.00)	3 (1.84)	3 (1.64)	0 (0.00)	4 (4.26)	4 (2.84)
<i>Acinetobacter</i> sp.	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.13)	1 (1.06)	2 (1.42)
<i>Providencia</i> sp.	0 (0.00)	0 (0.00)	0 (0.00)	2 (4.26)	0 (0.00)	2 (1.42)
<i>Candida</i> sp.	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.06)	1 (0.71)
<i>Enterococcus</i> sp.	0 (0.00)	1 (0.61)	1 (0.55)	1 (2.13)	0 (0.00)	1 (0.71)
Total	20 (100)	163 (100)	183 (100)	47 (100)	94 (100)	141 (100)

**Table 4.** Resistance profile of uropathogens isolated in samples of hospitalized patients in Nova Friburgo, in the period of July 2010 to November 2012 and July 2013 to June 2014.

Antibiotic	<i>E. coli</i> (93) n (%)	<i>Enterobacter</i> sp. (11) n (%)	<i>Proteus</i> sp. (10) n (%)
Amikacin	6 (6.45)	1 (9.09)	NT
Amoxicillin/ Clavulanic acid	22 (23.66)	6 (54.55)	6 (60.00)
Ampicillin	49 (52.69)	8 (72.73)	4 (40.00)
Ampicillin/ Sulbactam	1 (1.08)	NT	4 (40.00)
Aztreonam	4 (4.30)	3 (27.27)	2 (20.00)
Cefepime	6 (6.45)	3 (27.27)	1 (10.00)
Cefotaxime	6 (6.45)	2 (18.18)	NT
Ceftazidime	8 (8.60)	NT	1 (10.00)
Ceftriaxone	9 (9.68)	3 (27.27)	4 (40.00)
Cefuroxime	3 (3.23)	2 (18.18)	NT
Cephalothin	40 (43.01)	6 (54.55)	7 (70.00)
Ciprofloxacin	31 (33.33)	5 (45.45)	1 (10.00)
Gentamicin	8 (8.60)	4 (36.36)	1 (10.00)
Imipenem	2 (2.15)	NT	NT
Levofloxacin	29 (31.18)	5 (45.45)	NT
Meropenem	2 (2.15)	1 (9.09)	1 (10.00)
Nalidixic acid	5 (5.38)	1 (9.09)	NT
Nitrofurantoin	25 (26.88)	NT	7 (70.00)
Pipemidic acid	6 (6.45)	1 (9.09)	NT
Piperacillin/ Tazobactam	5 (5.38)	NT	1 (10.00)
Trimethoprim/ Sulfamethoxazole	40 (43.01)	6 (54.55)	9 (90.00)

NT: not tested.

## DISCUSSION

When the UTI is acquired in the hospital, the etiologic agents are quite diverse, composed predominantly *Enterobacteriaceae*, usually but not always *E. coli*, followed by *Proteus* sp., *Pseudomonas* sp., *Klebsiella* sp., *Enterobacter* sp., *Enterococcus* sp., and fungi, especially *Candida* sp.<sup>12,13</sup> In UTIs acquired in communities, *Escherichia coli* predominate, being isolated in 70% to 85% of cases. In our study, *E. coli* was the most prevalent microorganism isolated in both community and hospital UTIs, and showed considerable resistance against most of antibiotics used to treat UTIs.

Our results demonstrated that females (13-40 years old) are more susceptible to UTIs, corroborating with the literature.<sup>14,15</sup> *E. coli* from the outpatient samples were considerably resistant to nitrofurantoin. Recent international guidelines for the treatment of uncomplicated cystitis explicitly recognize the ecologic adverse effects of antimicrobial agents as an important factor for therapeutic choices.<sup>16</sup> Although these guidelines recommend avoiding fluoroquinolones, such as ciprofloxacin, they remain indicating agents such as nitrofurantoin, which has shown resistance.<sup>17</sup>

*Enterobacter* sp. was resistant to most antimicrobial

agents, and showed susceptibility only to gentamicin, quinolones, and ceftriaxone.

*Proteus* sp. showed resistance to ampicillin, cephalixin, trimethoprim - sulfamethoxazole and nalidixic acid, being susceptible to other antimicrobials.

All microorganisms isolated from outpatients in this work showed good sensitivity to antibiotics less frequently used in community UTI, such as second and third generation of cephalosporins (cefoxitin, ceftriaxone) and aminoglycosides (gentamicin).

At this work, bacteria isolated from nosocomial infections were more resistant to antimicrobials than microorganisms isolated from community infections. *E. coli* was 52.69% resistant to ampicillin and 43.01% to trimethoprim/sulfamethoxazole. More than 30% of *E. coli* isolates were resistant to ciprofloxacin, and even greater indices have been reported.<sup>18</sup>

These antimicrobials were widely used, and their indiscriminate use and self-medication can have caused the increase of resistance.<sup>19</sup> The development of antimicrobial resistance among gram-negative pathogens has been progressive and is increasing in bacteria isolated from both nosocomial and community-acquired UTI.<sup>20</sup> Contributing factors are the extensive use of antibiotics, both in human beings and animals, poor infection control, and the greatly increased global mobility of people, allowing the rapid spread of multidrug-resistant pathogens.<sup>21</sup>

Our data demonstrated that about a third of the strains isolated in the nosocomial environment were resistant to ciprofloxacin. Previous use of this antimicrobial can have induced resistance in these strains.

The use of ciprofloxacin as a first empirical treatment option for treatment of UTI is questionable, since this would select more resistant strains at the community setting and then, would be ineffective in the hospitals of the region where the our study was conducted.

Pathogens of particular concern include extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae* (ESBL), carbapenem-resistant *Enterobacteriaceae* (CRE), and multidrug-resistant *Pseudomonas aeruginosa*. Classic agents used to treat these pathogens have become outdated. Of the few new drugs available, many have already become targets for bacterial mechanisms of resistance.<sup>22</sup>

Beta-lactamases are bacterial  $\beta$ -lactams enzymes that inactivate by hydrolysis, resulting in inefficiency of antibiotics. An ESBL group is able to hydrolyze and cause resistance for a large variety of new  $\beta$ -lactams, including third generation cephalosporins and monobactams, but not against cephamycins and carbapenems. ESBLs producing bacteria are common in hospitalized patients, but have also been reported in positive cases of community-acquired infections.<sup>23</sup>

Treatment of these multiple drug resistant organisms is a deep scientific concern. At the level of a wider geographic scale, the incidence of ESBL-producing organisms is difficult to resolve due to various reasons, difficulty in detecting ESBL production and inconsistencies in reporting.<sup>24</sup>

In our study, ceftriaxone and carbapenems offered the best antimicrobial activity for outpatient strains, and the associate antimicrobials piperacillin/tazobactam and ampi-



cillin/sulbactam were most effective for nosocomial strains.

Until then, there are not regional studies published on the prevalence and antimicrobial susceptibility. These data are important for the surveillance of infections and to help in the clinical treatment.

Our data shows the importance of the study of prevalence and antimicrobial susceptible profiles of bacterial isolates at regional level. Thus, these results may contribute to better selection of antimicrobial for therapy of both hospital and ambulatorial-acquired UTIs in our community.

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